

Our Ref.: 2051-44  
P-1062-USA

# ***U.S. PATENT APPLICATION***

***Inventor(s):*** Bernard C. Sherman

***Invention:*** FOSINOPRIL SODIUM TABLET FORMULATION

***NIXON & VANDERHYE P.C.  
ATTORNEYS AT LAW  
1100 NORTH GLEBE ROAD  
8<sup>TH</sup> FLOOR  
ARLINGTON, VIRGINIA 22201-4714  
(703) 816-4000  
Facsimile (703) 816-4100***

## ***SPECIFICATION***

[illegible]

## 5

10 U.S. patent 5,006,344 explains that tablets comprising fosinopril sodium are relatively unstable when the tablets also comprise magnesium stearate as the lubricant. This patent further discloses that tablets with improved stability can be obtained by eliminating magnesium stearate and instead using as the lubricant either sodium stearyl fumarate or hydrogenated vegetable oil.

15

20    Tablets comprising fosinopril sodium are now sold in the United States under the tradename Monopril™. These tablets are made in accordance with the teaching of U.S. patent 5,006,344 and comprise sodium stearyl fumarate as the lubricant.

30 The object of the present invention is thus to find a lubricant for fosinopril sodium tablets other than sodium stearyl fumarate, that is effective as a lubricant, and that is relatively inexpensive.

## SUMMARY OF THE INVENTION

It has been found that both stearic acid and zinc stearate are effective  
5 lubricants for fosinopril sodium tablets.

Moreover, it has been surprisingly found that, unlike magnesium stearate and  
calcium stearate, neither stearic acid nor zinc stearate causes the tablets to  
be unstable.

10

The invention is thus a pharmaceutical tablet comprising fosinopril sodium  
along with either stearic acid or zinc stearate as the lubricant.

## 15 DETAILED DESCRIPTION OF THE INVENTION

In addition to fosinopril sodium as the active ingredient, and either stearic acid  
or zinc stearate as the lubricant, the tablet formulation will also comprise at  
least one other excipient as a filler and binder, such as, for example, lactose  
20 or microcrystalline cellulose. The preferred filler is lactose.

The tablet will also optionally comprise a disintegrant, such as, for example,  
starch, croscarmellose sodium, sodium starch glycolate, or crospovidone.  
The tablet will also optionally comprise other excipients, such as a colour  
25 agent. The tablet will also optionally contain another active ingredient, such  
as a diuretic.

The quantity of the lubricant as a percentage of the total tablet weight will  
preferably be from about 0.3 percent to about 4.0 percent.

30

The fosinopril sodium tablets of this invention can be prepared by conventional tablet forming techniques such as, for example, wet granulation and dry granulation. In the wet granulation process, the active ingredient or ingredients are mixed with some or all of the filler. This blend is then wet granulated with a solution of a binder in solvent. The resultant wet granulation is then dried and milled. The granules are then mixed with the remaining ingredients, which will include the lubricant, to produce the final mix, which is then compressed into tablets.

In the dry granulation process, the active ingredient or ingredients are mixed with the other ingredients without addition of any solvent, and thus without the need for drying. Again the final mix is compressed into tablets. The dry granulation approach is preferred as it is simpler and thus less costly.

The invention will be further understood from the following examples:

Example No:	1	2	3	4	5
Fosinopril Sodium	10.0	10.0	10.0	10.0	10.0
Lactose Anhydrous	188.0	188.0	188.0	186.0	188.0
Magnesium Stearate	2.0	X	X	X	X
Zinc Stearate	X	2.0	X	X	X
Calcium Stearate	X	X	2.0	X	X
Stearic Acid	X	X	X	4.0	X
Sodium Stearyl Fumarate	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>2.0</u>
	100.0	100.0	100.0	100.0	100.0

For each of the 5 examples, the ingredients in the proportions listed were mixed together. The powder mixture was then passed through a #40 screen and mixed again. The powder mixture was then compressed into tablets of weight 100 mg each, so that each tablet contained 10 mg of fosinopril sodium.

Tablets of each of the examples were stored at 60°C for two weeks and then tested by an HPLC method to determine the degradation products as a percentage of the initial fosinopril sodium content.

The results were as follows:

<u>Example No.</u>	<u>Lubricant</u>	<u>% Degradation Products</u>
1	Magnesium Stearate	46.2%
2	Zinc Stearate	1.7%
3	Calcium Stearate	75.5%
4	Stearic Acid	2.1%
5	Sodium Stearyl Fumarate	2.8%

For example 1, using magnesium stearate, the degradation products total 46.2%, whereas for example 5, using sodium stearyl fumarate, the degradation products total only 2.8%. This confirms the teaching of U.S. patent 5,006,344 that stability is very much improved by using sodium stearyl fumarate as lubricant instead of magnesium stearate.

Example 3, using calcium stearate, shows degradation products totalling 75.5%, which is even worse than obtained using magnesium stearate.

However, example 2, using zinc stearate, shows degradation products totalling only 1.7% and example 4, using stearic acid, shows degradation products totalling only 2.1%.

It is thus found that, while degradation rate is high when either magnesium stearate or calcium stearate is used as lubricant, the degradation rate is low when either zinc stearate or stearic acid is used as lubricant.